REMARKS

By the present amendment, claims 2-9, 13-15, and 23-29 are hereby cancelled without prejudice. Accordingly, claims 1, 10-12, and 16-22 are pending, of which claim 1 is the sole remaining independent claim. Claims 1, 10, and 11 are amended to more particularly point out and distinctly claim the subject matter of the invention. Support for the amendments may be found in the original claims and in the specification. No new matter is added into the case by any of the amendments.

In the Office Action, Claims 1, 3-7, 9-14, 17-22, and 24-29 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by U.S. Patent No. 4,680,262 to Bochner et al. ("Bochner"). Claims 1, 8, 24, and 28 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bochner in view of U.S. Patent No. 6,613,335 to Ruelle ("Ruelle"). Claims 1 and 16 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bochner in view of U.S. Patent No. 6,337,205 to Wisniewski ("Wisniewski").

Applicants respectfully traverse all rejections of the present claims, and request reconsideration and favorable action in light of the above amendments and the foregoing remarks.[1]

A. No Claims Anticipated by Bochner or Any Other Known Prior Art.

Claims 2-9, 13-15, and 23-29 are cancelled, thereby rendering moot any/all rejections of those claims based on Bochner or any other cited art.

Claim 1 is the sole independent claim. This claim is directed to a process for making a recombinant polypeptide. The claim recites, among other things, fermenting a prokaryotic host cell in a fermentation medium to cause the polypeptide to be expressed and then secreted into periplasm of the host cell. The fermentation medium is then concentrated prior to completion of fermentation and after or in conjunction with secretion of expressed polypeptide into the host cell's periplasm in order to make a concentrated fermentation medium containing the host cell whose periplasm contains the expressed polypeptide. Following or in conjunction with concentration of the medium, the fermentation process is interrupted, prior to completion of the fermentation, and the medium is then maintained under non-lethal conditions for a hold period

[1] All rejections of claims cancelled herein are rendered moot. This includes Claims 2-9, 13-15, and 23-29 as mentioned in paragraph 1.

ranging from about 1 hour to about 72 hours at a temperature ranging from about 4°C to about 25°C and a pH ranging from about 4 to about 10.

Following the interruption hold, recombinant polypeptide expressed in the cell periplasm in the concentrated fermentation medium is recovered by a suitable procedure to provide an increased yield of polypeptide compared to processes that carry fermentation to completion. See, e.g., Table 1 of Example 1 and Examples 2 and 3. Yield/quality improvements translate to substantial productivity gains for large-scale industrial production of a range of recombinant protenaceous materials.

Claim 1 patentably distinguishes from the cited art by, among other things, its requirement that fermentation of host cells in a concentrated fermentation medium be prematurely interrupted, and that the medium then be held under defined conditions that are not lethal to the cell. As a result, increased yields of recombinant polypeptide are obtained relative to conventional processes that take fermentation to full completion and exhaustion of significant biological activity. While the mechanism behind the invention is not fully understood, it is believed that secretion of desired polypeptides in cell periplasm may actually peak well ahead of completion of the process of cell fermentation, after which peak polypeptides secreted into the periplasm somehow deteriorate or become more difficult to extract; or perhaps the process even reverses after a peak as the fermentation continues. Nothing in the known prior art even remotely suggests this.

Bochner is said to anticipate Applicants' claimed process, however, concept of Bochner is far removed from what Applicants have discovered. In particular, Bochner does not teach "interruption" of a fermentation process before completion of the process, much less concentration of a fermentation medium prior to and/or in conjunction with interruption of the fermentation. Bochner teaches to first grow the cells to a "desired point of growth" (indicated as accumulating protein to a "maximum" level at col. 4, lines 41-45), after which the cells are killed by exposure to heat and alcohol. Bochner then requires freezing and thawing/dilution of the dead cell concentrate as an essential step.

Accordingly, a key distinction between Applicants' process and Bochner's process is the fact that Bochner requires application of lethal heat conditions and alkanol exposure to kill the cells after completion of fermentation and prior to any concentration step. While killing

cells does stop growth, it is not a step of "interrupting" as called for in Claim 1. The interruption called for in the present case is in the sense of "suspending" fermentation of cells under specified, non-lethal conditions. These defined conditions simply hold, suspend, or significantly slow down to virtually nil the fermentation process. These suspension or "hold" conditions are not conditions intended to kill the cells, and there is NO suggestion whatsoever in Bochner that any interruption of fermentation should occur before cell growth or fermentation is finished.

Another important difference is that Bochner freezes the dead cells at a temperature of -20°C to -80°C after killing them, and prior to any further processing or extraction.

So, it is apparent that Bochner teaches (at least in a preferred embodiments) to kill the cells with heat and an alkanol, after which the residue is concentrated, frozen, thawed, and then finally processed to extract a protein of interest. In contrast, Applicants claim a process in which fermentation of concentrated medium is substantially suspended after recombinant polypeptide has been secreted into the cell periplasm, and where the medium is maintained under non-lethal, quiescent conditions, after which the desired polypeptide is harvested with an improved yield compared to conventional processes that complete fermentation and associated cell growth. Applicants' entire claimed process can take place at temperatures above about 4°C and without requiring any additional organic or other reagents that would kill cells. Bochner says that killing the cells doubles the recovery of desired protein. If the cells are not killed at completion of fermentation, they are immediately processed to recover the protein of interest. The latter is, of course, less preferred in the Bochner approach, but is still far from the concept employed by Applicants.[2] See, Col. 5, lines 18-21. Thus, Bochner teaches directly against Applicants' claimed invention.

Applicants' claimed process therefore represents a significant improvement in heretofore known protein preparation techniques, since high yields of a protein of interest can now advantageously be recovered in fewer steps, using fewer resources with less extreme conditions than previously said to be required.

[2] The only alternative to the preferred embodiment of killing the cells is to PROCESS the cells quickly after cell growth is finished, but this is less preferred. Neither "killing" or "processing quickly" suggests interrupting fermentation and moving to a non-lethal "hold" conditions in accordance with the present claims.

Applicants' approach is counterintuitive. No known evidence or prior art suggests that recombinant polypeptide yields in a fermentation-based production system can be improved by prematurely interrupting the fermentation process with the medium in a concentrated state, and then holding the medium containing cells with the polypeptide secreted into the periplasm under quiescent, non-lethal conditions for a period of time, after which periplasmic polypeptide is harvested in a better yield than if the fermentation had been allowed to go to completion. This is not an obvious thing to do.

Claims 5, 8, 10-12, and 16-22 depend from claim 1 and add important limitations to the claimed subject matter. Since claim 1 is shown to patentably distinguish over Bochner, the reference cannot anticipate or suggest the dependent claims, either. Accordingly, reconsideration and allowance of claims 1, 5, 8, 10-12, and 16-22 are respectfully requested.

B. Claims 1 and 8 are Patentably Distinguish Over the Cited References.

Claims 1, 8, 24, and 28 are rejected as allegedly unpatentable over Bochner in view of Ruelle, however, claims 24 and 28 are cancelled, so their rejections are moot. As discussed in part above, Bochner fails to provide all of the elements and limitations of claims 1 and 8, and it certainly cannot be said to suggest the subject matter of these claims. The combination of Bochner with Ruelle is likewise deficient in suggesting the limitations of claims 1 and 8. Hence, a person having ordinary skill in the art would not regard the presently amended claims as obvious from the teachings of the combination, nor would a person of skill view the noted portions of these references as an "obvious" combination, given the lack of any objectively reasonable motivation or other predisposition to combine them in the manner imagined by the Examiner.

Ruelle, like Bochner, fails to disclose a process for the preparation of a recombinant polypeptide that is even remotely similar to that called for in independent Claim 1. Specifically, neither Bochner nor Ruelle disclose that a fermentation medium containing a periplasmic polypeptide should be concentrated by centrifugation, micro filtration, or otherwise, much less that any such processing be done prior to any interruption of fermentation of the host cell in the fermentation medium under non-lethal hold conditions before fermentation is completed according to claim 1. Bochner and Ruelle are also both deficient in

disclosing any interruption conditions employed in claim 1.

Accordingly, the combined references do not even arguably suggest or in any way render the present claims obvious according a proper application of Section 103. Reconsideration and allowance of claims 1 and 8 are hereby respectfully requested.

C. Claims 1 and 16 are Patentably Distinct Over the Cited References.

Claims 1 and 16 are also said to be obvious from Bochner combined with Wisniewski. As discussed above, Bochner fails to suggest the elements and limitations of claims 1 and 16. Likewise, no objectively reasonable basis has been established as to why a person of ordinary skill would be motivated to combine these references in the manner imagined and, in any event, Bochner and Wisniewski considered together still do not provide all of the elements and limitations of the presently amended claims.

Wisniewski, like Bochner, fails to disclose a process for making a recombinant polypeptide as called for in independent claim 1. Specifically, neither Bochner nor Wisniewski disclose a method for making a recombinant polypeptide in which a transformed cell containing a recombinant expression system for expressing a recombinant polypeptide and secreting polypeptide into the cell periplasm upon fermentation of the cell in a fermentation medium is fermented in the fermentation medium so as to cause expression of the polypeptide in the cell's periplasm, and where the fermentation medium is concentrated by centrifuging, micro filtration, or the like, after or during which the fermentation is interrupted and held under the non-lethal conditions of time, temperature, and pH according to the claims for recovery of increased yields of the polypeptide of interest compared to conventional processes in which the fermentation is allowed to go to completion.

Also, Wisniewski, like Bochner, is deficient in disclosing the particular hold conditions requirement claimed in Claim 1. In fact, Wisniewski uses cryopreservation systems and methods which, by definition, operate at extreme temperatures far below freezing. No combination of steps from Bochner and Wisniewski can reasonably be said to disclose the non-lethal interruption hold conditions of Claim 1, where the host cell is maintained in an "interrupted" fermentation medium at a temperature ranging from about 4°C to about 25°C.

Thus, the combined references do not render the present claims obvious because, among other things, there is no motivation or incentive to combine them in the manner indicated so as to provide a method according to that claimed by Applicants but, even if there was (and there is not), no combination of steps from the references contains all the elements and limitations of the present claims. Reconsideration and allowance of claims 1 and 16 are hereby respectfully requested.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 12-2355.

Respectfully submitted,

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